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**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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*Ex parte* MARIA ADELE PACCIARINI, OLGA VALOTA, and DAVID KERR[1]

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Appeal 2008-5301[2]
Application 09/786,998
Technology Center 1600

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Decided:[3] February 25, 2009

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Before DONALD E. ADAMS, LORA M. GREEN, and MELANIE L. McCOLLUM, *Administrative Patent Judges*.

McCOLLUM, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The real party in interest is Nerviano Medical Sciences S.r.l. (App. Br. 2).
[2] Oral Hearing held February 3, 2009.
[3] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is an appeal under 35 U.S.C. § 134 involving claims to a pharmaceutical composition and a treatment method. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

## STATEMENT OF THE CASE

Claims 13, 14, and 18-31 are pending and on appeal. We will focus on claims 13, 18, 19, 24, 25, 28, and 31, which read as follows:

13. A pharmaceutical composition which comprises as an active principle MMDX and a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection through the hepatic artery.

18. A method of treating a human liver tumor which comprises the intrahepatic administration of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) to a patient in need thereof.

19. A method for reducing methoxymorpholino doxorubicin systemic exposure of a patient suffering from a liver cancer which comprises the intrahepatic administration of a therapeutically effective amount of methoxymorpholino doxorubicin (MMDX) to said patient.

24. A method according to claim 18, wherein MMDX is administered as an infusion of from about 15 minutes to about 30 minutes every 4 weeks.

25. A method according to claim 18, wherein MMDX is administered as a 5-10 minute bolus every 8 weeks.

28. A method according to claim 1, wherein MMDX is administered in a dose ranging from about 100 mcg/$m^2$ to about 1000 mcg/$m^2$.

31. A method of treating human liver tumor, which comprises the intrahepatic administration of a therapeutically effective amount of a pharmaceutical composition which comprises as an active principle methoxymorpholino doxorubicin (MMDX) and a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection through the hepatic artery.

The Examiner relies on the following references:

Bargiotti et al., US 5,304,687, Apr. 19, 1994 (hereinafter "Bargiotti");

Jörn-Sven Kühl et al., *Effects of the methoxymorpholino derivative of doxorubicin and its bioactivated form versus doxorubicin on human leukemia and lymphoma cell lines and normal bone marrow*, 33 CANCER CHEMOTHER. PHARMACOL. 10-16 (1993) (hereinafter "Kuhl");

Y. Takayasu et al., *Large-dose intra-arterial injection of lipiodol in liver cancer*, 15 GAN TO KAGAKU RYOHO 2562-67 (1988) (for consistency with the Examiner and Appellants, hereinafter "Nakamura"); and

V.A. Gorbunova, *Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver*, 12 SOV. MED. 66-68 (1990) (hereinafter "Gorbunova").

Appellants rely on the following reference:

Edward Chu and Vincent T. DeVita, Jr., *Principles of Cancer Management: Chemotherapy*, in CANCER: PRINCIPLE AND PRACTICE OF ONCOLOGY 289-306 (Ch. 17) (hereinafter "DeVita").

Claims 13, 14, and 18-31 stand rejected under 35 U.S.C. § 103(a) as obvious in view of Bargiotti, Kuhl, Nakamura, and Gorbunova (Ans. 3).

The Examiner relies on Bargiotti for teaching "morpholino derivatives of anthracyclines [including] methoxy morpholino doxorubicin" and that these "derivatives are shown to inhibit solid tumors such as human carcinoma with intravenous and oral route" (*id.*).

The Examiner relies on Kuhl for teaching "that the methoxymorpholino derivative of doxorubicin has a broad-spectrum

antitumor activity and is . . . activated in the liver to a metabolite which crosslinks to DNA and is 10 times more potent" (*id.* at 3-4.)

The Examiner relies on Nakamura for teaching that "intra-arterial infusion of lipiodol (iodized oil) and adriamycin (same as doxorubicin) showed remarkable therapeutic effects for advanced cancer" (*id.* at 4).

The Examiner relies on Gorbunova for teaching that "intra hepatic arterial infusion chemotherapy allows for creating a super high concentration of an antitumor agent in the organ affected by the tumor" (*id.*).

The Examiner concludes that it would have been obvious "to make a composition comprising methoxymorpholino doxorubicin [MMDX] with iodized oil and use the same in a method of treating a human liver tumor and reducing systemic exposure as instantly claimed" (*id.*). In particular, the Examiner argues that it "is logical that lipiodol (iodized oil) be administered in combination with MMDX since it has shown therapeutic effects when administered with the closely related adriamycin (adriamycin is the Trade name for doxorubicin and structurally very close to MMDX)" (*id.* at 4-5). In addition, the Examiner concludes that it "is well within the purview of one of ordinary skill in the art to adjust dosages and the frequency of administration based on that taught in the prior art" (*id.* at 4)

The Examiner also argues that "[o]ne of ordinary skill in the art would have been motivated to use MMDX . . . in hepatic artery administration since [the] prior art recognizes that hepatic artery administration of doxorubicin is beneficial in treating tumor" (*id.*). In addition, the Examiner argues that "[h]epatic arterial administration . . . creates super high concentrations in the organ affected" and this "localized administration is

beneficial for reducing systemic exposure and reducing tumor volume in the liver" (*id.*).

ISSUES

The issues on appeal are:

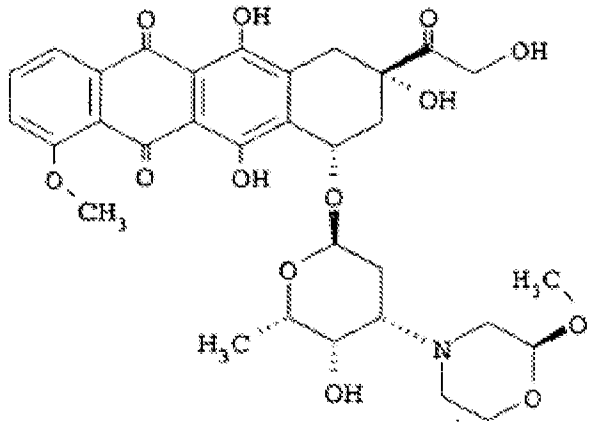
Did the Examiner set forth a prima facie case that: (a) it would have been obvious to combine MMDX with lipiodol; and (b) it would have been obvious to treat liver cancer by the intrahepatic administration of MMDX?

If so, did Appellants overcome the Examiner's prima facie case of obviousness with a showing of unexpected results?

FINDINGS OF FACT

1. The Specification discloses the "use of methoxymorpholino doxorubicin for the treatment of a liver cancer" (Spec. 1: 6-7).

2. "Methoxymorpholino doxorubicin (MMDX . . . ) of formula



is a . . . doxorubicin derivative obtained with the substitution of the $-NH_2$ at position 3' in the sugar moiety with a methoxymorpholino group" (*id.* at 1: 11-16).

3. The Specification discloses that MMDX "differs from most anthracyclines in being highly potent when administered *in vivo*, the optimal i.v. dose being at least 80 fold less than that of doxorubicin" (*id.* at 2: 7-9).

4. The Specification also states:

> It would be . . . desirable to establish drug delivery strategies to avoid the high i.v. dosages of MMDX *presently believed to have an antitumor activity at the hepatic level* and to improve the antitumor efficacy of MMDX against a primary liver cancer and liver metastases.
>
> There is a need to achieve high MMDX concentration at the hepatic tumor site, while reducing systemic exposure and hence toxicity.
>
> The present invention fulfills such a need by providing a new method for administration of MMDX to a patient suffering from a liver tumor which reduces the MMDX amount without decreasing the MMDX's antitumor activity at the hepatic tumor site by directly injecting MMDX into the hepatic artery.

(*Id.* at 7: 13-25 (emphasis added).)

5. In addition, the Specification discloses mixing "the appropriate dose of MMDX . . . with a suitable amount of an agent which remains selectively in a liver tumor after its injection through the hepatic artery," such as iodized oil (LIPIODOL®) (*id.* at 8: 30 to 9: 9).

6. Bargiotti discloses anthracycline glycosides including MMDX in both the (S) and the (R) configurations (Bargiotti, col. 1, ll. 11-65).

7. Bargiotti states that the disclosed anthracycline glycosides are antitumor agents (*id.* at col. 5, ll. 27-30).

8. In particular, Bargiotti discloses that, in mice bearing Doxorubicin-resistant leukemia, (S)- and (R)-MMDX are "active and more potent that Doxorubicin" (*id.* at col. 11, ll. 42-61).

9. In addition, Bargiotti discloses that (S)-MMDX was shown to inhibit solid tumors, specifically murine and human mammary carcinomas (*id.* at col. 11, ll. 65-68, & col. 12, Tables 5-6).

10. Kuhl discloses that MMDX "has recently entered clinical trials because of its broad spectrum of preclinical antitumor activity and non-cross-resistance in multidrug-resistant (MDR) tumor models" (Kuhl, Abstract).

11. Kuhl also discloses that "MMDX is activated in the liver to a >10 times more potent metabolite that cross-links DNA" (*id.*).

12. In addition, Kuhl discloses that "MMDX was approximately 3-100 times more active than DOX [(doxorubicin)], and [bioactivated MMDX] was 10-1,000 times more potent than DOX" (*id.*).

13. Specifically, Kuhl discloses that "MMDX and its bioactivated form . . . are highly active against [the tested] panel for human leukemia and lymphoma cell lines" (*id.*).

14. Additionally, Kuhl states that MMDX was dissolved in ethanol (*id.* at 11).

15. Nakamura discloses the "[e]ffects of lipiodol (LPD) on liver functions . . . in 130 patients with primary and metastatic liver cancer," as well as the effects of anticancer agent, Adriamycin (ADM) (Nakamura, Abstract).

16. Nakamura discloses that "the therapeutic effects of intraarterial infusion of ADM-LPD emulsion for advanced cancer . . . are remarkable" (*id.*).

17. It is undisputed that Adriamycin is the tradename for doxorubicin (Ans. 5; *see also* App. Br. 13).

18. Gorbunova discloses that, in the treatment of hepatic cancer, the "use of intrahepatic arterial infusion chemotherapy (IHAIC) techniques . . . allow[s] creating super high concentrations of an antitumor agent in the organ affected by the tumor and increasing frequency of the objectively recorded effects" (Gorbunova, Abstract).

PRINCIPLES OF LAW

"In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (1995) (internal quotations omitted). "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, ___, 127 S.Ct. 1727, 1742 (2007). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at ___, 127 S. Ct. at 1739.

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

*In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

"[O]bjective evidence of nonobviousness includes . . . unexpected results created by the claimed invention." *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). "It is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). In addition, *expected* beneficial results are not evidence of nonobviousness. *See In re Skoner*, 517 F.2d 947, 950 (CCPA 1975).

ANALYSIS

Nakamura discloses a composition for treating liver cancer comprising doxorubicin and lipiodol, which is an agent that remains selectively in a tumor after its injection through the hepatic artery (Findings of Fact (FF) 15-17 & 5). Kuhl discloses that MMDX, a methoxymorpholino derivative of doxorubicin, has a "broad spectrum of preclinical antitumor activity" (FF 10 & 2). Although Kuhl specifically relates to leukemia and lymphoma (FF 13), Bargiotti discloses that MMDX has also been shown to inhibit solid tumors (FF 6-9). We conclude that the Examiner has set forth a prima facie case that it would have been obvious to form a composition comprising MMDX and lipiodol. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l v. Teleflex Inc.*, 550 at ___, 127 S. Ct. at 1739. In addition, we conclude that the Examiner has set forth a prima facie case that it would have been obvious to use the resulting composition to treat liver cancer.

Furthermore, Gorbunova discloses the use of intrahepatic arterial infusion in the treatment of liver cancer (FF 18). Based on this teaching, we

also conclude that the Examiner has set forth a prima facie case that it would have been obvious to treat liver cancer by the intrahepatic administration of the MMDX-lipiodol composition.

*With regard to claim 13*, Appellants argue:

> Bargiotti . . . does not disclose or remotely suggest a pharmaceutical composition which includes MMDX and a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection. Moreover, this reference does not provide any teaching or suggestion of administrating an MMDX composition or indeed any morpholino derivative pharmaceutical composition within the scope of this reference into the hepatic artery.

(App. Br. 11.) Appellants also argue that Kuhl does not disclose "providing a MMDX composition with a pharmaceutically acceptable agent which remains selectively in a liver tumor after its injection through the hepatic artery" (*id.*). In fact, Appellants argue:

> The teaching of Kuhl et al. is away from Claim 13 . . . insofar as the Kuhl et al. disclosure of an MMDX composition is limited to the recitation of examples, at Page 11, in which MMDX is disclosed in a composition. That composition, however, combines MMDX with ethanol. That sole composition teaching is away from Claim[] 13 . . . because it is well known to those skilled in the art that such a composition, which is recited to be retained in the liver, will cause cirrhosis of the liver given the notorious biological effect of ethanol in effectuating such an outcome.

(*Id.* at 12.)

We are not persuaded. First, claim 13 does not require administrating an MMDX composition into the hepatic artery. Instead, claim 13 is directed to a composition comprising MMDX and a pharmaceutically acceptable

agent that has the property of remaining selectively in a liver tumor if it is injected through the hepatic artery.

Second, we do not agree that Kuhl teaches away from the composition of claim 13. As noted by the Examiner, Kuhl combines MMDX with ethanol (FF 14). Even if it would not have been obvious to combine the MMDX-ethanol combination with an agent that remains selectively in a liver tumor, we do not agree that Kuhl teaches away from combining MMDX with such an agent.

Third, the Examiner is not relying on Bargiotti or Kuhl to teach a composition comprising a pharmaceutically acceptable agent that remains selectively in a liver tumor. Instead, Nakamura is relied on for teaching this feature (Ans. 4).

In addition, Appellants argue that Nakamura does not teach or suggest MMDX (App Br. 12). However, because the Examiner is not relying on Nakamura to teach or suggest MMDX, we are not persuaded by this argument.

Appellants also argue that Nakamura "is not combinable with the principal Bargiotti et al. reference insofar as Bargiotti et al. is limited to morpholino derivatives of anthracyclines. DOX, the sole compound within the scope of Nakamura et al., is not a morpholino derivative of an anthracycline." (App. Br. 13.)

We are not persuaded. Nakamura discloses that the combination of doxorubicin and lipiodol had a remarkable therapeutic effect on advanced cancer (FF 16). Bargiotti, as well as Kuhl, discloses that MMDX, a derivative of doxorubicin, also has antitumor activity (FF 6-13 & 2). In fact,

Bargiotti and Kuhl both indicate that MMDX may actually be more effective that doxorubicin (FF 8 & 11-12). Thus, we agree with the Examiner that it would have been obvious to combine MMDX with lipiodol.

In addition, Appellants argue that Gorbunova "provides no weight, given its teaching of a chemically distinct compound" (App. Br. 13). The Examiner relies on Gorbunova for teaching intrahepatic administration of chemotherapy (Ans. 4). Given that claim 13 does not require intrahepatic administration, we conclude that this reference is not even needed to render claim 13 obvious.

Appellants also "observe that the optimum intravenous dose of MMDX is at least eighty times less than that of DOX" (Reply Br. 2-3). Appellants argue that this "dramatic difference in functionality of MMDX demonstrates far superior and unexpected efficacy over DOX, *in vivo*. This unexpected efficacy certainly would not have been appreciated by the skilled artisan at the time of the invention. As such, this remarkable efficacy rebuts any presumption of structural or functional obviousness." (*Id.* at 3.)

We are not persuaded. The Specification states that MMDX "differs from most anthracyclines in being highly potent when administered *in vivo*, the optimal i.v. dose being at least 80 fold less than that of doxorubicin" (FF 3). From the context of this statement, it is not clear whether the inventors intended this to be a statement of the prior art or a statement of an unexpected result, particularly since the focus of their invention appears to be the intrahepatic administration of MMDX rather than intravenous administration (FF 4). However, even if it was intended to be a statement of an unexpected result, given that Kuhl discloses that "MMDX was

approximately 3-100 times more active than DOX [(doxorubicin)], and [bioactivated MMDX] was 10-1,000 times more potent than DOX" (FF 12), we do not agree that this statement would be sufficient to rebut the prima facie case of obviousness.

*With regard to claim 18*, Appellants argue that "none of the applied references teach the administration of MMDX in the treatment of a human liver tumor wherein a therapeutic amount of that compound is intrahepatically administered to a patient in need thereof" (App. Br. 13).

In particular, Appellants argue that Bargiotti "merely discloses MMDX as a promising compound useful in providing antitumor activity in the treatment of murine tumors" (*id.* at 14). In addition, Appellants argue that Kuhl "merely discloses in vitro activity data suggesting that in tests of human leukemia and lymphoma cell lines MMDX was more sensitive than DOX" (*id.*). Appellants argue:

> Those skilled in the art are aware that such data as that provided in Kuhl et al. is not definitive of tumor specificity. That is, no disclosure is made in Kuhl et al. evidencing superior tumor reduction in any mammal. Indeed, the only teaching in Kuhl et al. is an in vitro showing of effectiveness against certain blood tumors. One skilled in the art would not thus be presented with a reasonable expectation of success upon using MMDX in the treatment of liver tumors.

(*Id.*) Appellants also argue that DeVita teaches that "agents useful in the treatment of blood tumors, such as leukemia and lymphoma, have no therapeutic efficacy against solid tumors" and therefore "further emphasizes the irrelevance of Kuhl. . . . Chemotherapeutic agents, such as MMDX, are tumor-specific and the results of chemotherapy depend on tumor growth characteristics and on the tumor's individual resistance to the drug." (*Id.* at

14-15.) Thus, Appellants argue that "the combined teaching of [Bargiotti and Kuhl] do not . . . suggest treatment of liver tumors by administration of MMDX, let alone intrahepatic introduction of that drug" (*id.* at 15).

We are not persuaded. We agree with Appellants that neither Bargiotti nor Kuhl specifically teach the treatment of liver cancer. However, given the fact that Kuhl describes MMDX as having "broad spectrum . . . antitumor activity" (FF 10), Bargiotti specifically discloses the inhibition of solid tumors (FF 9), and Nakamura discloses that a derivative of MMDX can be used to treat liver cancer (FF 15-17), we agree with the Examiner that there would have been a reasonable expectation for success. In particular, even assuming that DeVita generally teaches that "agents useful in the treatment of blood tumors, such as leukemia and lymphoma, have no therapeutic efficacy against solid tumors," Bargiotti teaches that MMDX inhibits solid tumors, specifically carcinomas (FF 9).

With regard to disclosing the intrahepatic administration of MMDX, the Examiner relies on Gorbunova (Ans. 4). Appellants have not adequately explained why it would not have been obvious to combine Gorbunova with the other references in order to suggest intrahepatic administration of MMDX.

In addition, Appellants argue:

> Kuhl et al. teaches that MMDX is activated in the liver to a highly active metabolite. This teaching . . . suggests that MMDX is transformed in the body into highly cytotoxic metabolites. Moreover, the Examiner admits that Gorbunova et al. teaches that intra-arterial infusion chemotherapy allows for the creation of extremely high concentrations of the antitumor agents in the organ affected by the tumor. Therefore, in view of the teachings from the prior art that extremely high

> concentrations of MMDX would be created around the liver by intrahepatic administration of MMDX, and MMDX would be transformed into highly cytotoxic metabolites, one skilled in the art would not have been motivated to even attempt to try to use MMDX in an intrahepatic administration for the treatment of liver tumors . . . , since such treatment would cause significant toxicity to the human body. Stated differently, the cited art provides a clear teaching away from the presently claimed invention.

(Reply Br. 4-5.)

We are not persuaded. The purpose of chemotherapy is to create a cytotoxic environment. Based on the noted teachings in Kuhl and Gorbunova, Appellants may have been motivated to use a lower amount of MMDX than doxorubicin or than would be used if MMDX was being administered by a route other than intrahepatic administration. However, we do not agree that the potential for significant toxicity would teach away from the method of claim 18.

*With regard to claim 19*, Appellants additionally argue that "even if there were a showing, by the combined teaching of the applied references, suggesting [treating liver cancer by the intrahepatic administration of MMDX], the showing of the unexpected result of reduced systemic exposure to MMDX, occasioned by its intrahepatic administration, rebuts any presumption of obviousness" (App. Br. 17). In particular, Appellants argue:

> The experimental protocol provided in the specification of the application on appeal establishes that a reduced concentration of MMDX, an admitted toxic compound, is required to treat liver cancer when administered intrahepatically through the hepatic artery. Thus, even if MMDX treatment of humans suffering from cancer were disclosed in the prior art, which is not the case, . . . its intrahepatic administration would still be

> patentable based on the unexpected result of reduced systemic exposure to the toxic chemotherapeutic agent, MMDX.

(*Id.*)

We are not persuaded. Gorbunova discloses that, in the treatment of hepatic cancer, the "use of intrahepatic arterial infusion chemotherapy (IHAIC) techniques . . . allow[s] creating super high concentrations of an antitumor agent in the organ affected by the tumor" (FF 18). Thus, we agree with the Examiner that, "[s]ince intra-arterial administration creates a high concentration in the organ affected by the tumor, one of skill in the art would expect reduced systemic exposure of the active agent . . . via intrahepatic arterial infusion" (Ans. 8). In particular, because intrahepatic administration creates a high concentration of antitumor agent at the site of the cancer, less overall antitumor agent would be required to achieve the same effect and therefore a reduced systemic exposure would be expected.

*With regard to claims 24 and 25*, Appellants argue that the "showing presented in the specification establish not only the effectiveness of the general method of treatment of human liver cancer but also at concentrations consistent with reduced systemic exposure to MMDX" (App. Br. 18). In particular, Appellants argue that claims 24 and 25 "provide specific treatment regimes . . . which provide . . . unexpectedly improved results" (*id.*).

We are not persuaded. In particular, for the reasons discussed above, we do not agree that Appellants have provided sufficient evidence of unexpected results for administering MMDX by intrahepatic administration, much less for the treatment regimes recited in claims 24 and 25.

*With regard to claims 28-30*,[4] Appellants argue that "the dosage range[s] set forth in [these claims], which is predicated upon both therapeutic effectiveness and minimizing of toxicity problems, would . . . be a patentable invention in view of the obtaining of these unexpected results" (App. Br. 19). However, we do not agree that Appellants have provided sufficient evidence of unexpected results for administering MMDX by intrahepatic administration, much less for the dosage ranges recited in claims 28-30.

*With regard to claim 31*, Appellants argue that it should "be appreciated that the requirement that the MMDX pharmaceutical composition remains selectively in the liver tumor after its injection through the hepatic artery is totally undisclosed in any of the applied references" (App. Br. 19). We are not persuaded. Claim 31 recites "a pharmaceutically acceptable agent which remains selectively in the liver tumor after its injection through the hepatic artery." Although Nakamura, at least in the English Abstract, does not recite that lipiodol is an "agent which remains selectively in the liver tumor after its injection through the hepatic artery," the Specification discloses that it is such an agent (FF 5). Thus, based on the disclosure in Nakamura, we agree with the Examiner that it would have been obvious to administer lipiodol, together with an antitumor agent, to treat a human liver tumor.

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[4] It is noted that claims 28-30 depend from claim 1, which is no longer pending in this application.

## CONCLUSION

The Examiner has set forth a prima facie case that: (a) it would have been obvious to combine MMDX with lipiodol; and (b) it would have been obvious to treat liver cancer by the intrahepatic administration of MMDX. In addition, Appellants have not provided sufficient evidence of unexpected results to overcome the Examiner's prima facie case of obviousness.

We therefore affirm the rejection of claims 13, 18, 19, 24, 25, and 28-31. Claim 14 and claims 20-23, 26, and 27 have been argued with claims 13 and 18, respectively, and therefore fall with claims 13 and 18. 37 C.F.R. § 41.37(c)(1)(vii).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

## AFFIRMED

LP

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